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26th July 2004

Applicant : HART, John Ernest
Serial number : 09/856,944
Assistant Commissioner for Patents
Washington, D. C. 20231

DECLARATION OF PROFESSOR IAIN JAMES CLARKE UNDER 37 CFR S. 1.132

1. My name is Iain James CLARKE and I am currently Senior Principal Research Fellow at Prince Henry's Institute of Medical Research, Clayton, Victoria, Australia, conducting research in the field of neuroendocrinology. I am also Honorary Professor, Department of Physiology, Monash University, Clayton, Victoria, Australia and Director of Biological Resources of Prince Henry's Institute.

2. I received a B.Agric.Sci from Massey University in 1971 and a M.Agric.Sci from the same Institution in 1973. I received a PhD in animal reproduction, endocrinology and behaviour in 1977 from Edinburgh University, the work having been completed in the Medical Research Council Unit of Reproductive Biology. I was appointed to my present post as Senior Principal Research Fellow in 1998.

3. The major part of my career has been in the field of reproductive endocrinology, generally involving the elucidation of the properties and behaviour of hormones in animals. I have published 350 papers or chapters in learned journals or books and I am a member of the Endocrine Society of the US amongst other Societies. I am Program Organising Chairman for the International Neuroendocrine Federation and am active in the organisation of other meetings around the Globe. An example of my international standing is my recent paper presented to The Endocrine Society in the TransPacific Symposium of this year's meeting.

4. I have carried out research on ovulation in sheep and humans, as evidenced in the following papers:-

CLARKE, I.J., SCARAMUZZI, R.J. and SHORT, R.V. Ovulation in prenatally androgenized ewes. *J. Endocrinol.* 73: 385-389, 1977.

VAN LOOK, P.F.A., CLARKE, I.J., DAVIDSON, W. and SCARAMUZZI, R.J. Ovulation and lambing rates in ewes actively immunized against androstenedione. *J. Reprod. Fert.* 53: 129-130, 1978.

CLARKE, I.J., FRASER, H.M. and Mc NEILLY, A.S. Active immunization of ewes against luteinizing hormone releasing hormone, and its effects on ovulation and gonadotrophin, prolactin and ovarian steroid secretion. *J. Endocrinol.* 78: 30-47, 1978.

SCARAMUZZI, R.J., BAIRD, D.T., CLARKE, I.J., MARTENSZ, N.D. and VAN LOOK, P.F.A. Ovarian morphology and the concentration of steroids during the oestrous cycle of sheep actively immunized against androstenedione. *J. Reprod. Fert.* 58: 27-35, 1980.



Director Professor Evan Simpson PhD Deputy Director Professor Jock Findlay AM PhD DSc
Prince Henry's Institute of Medical Research is a designated World Health Organization Collaborating Centre for Research in Human Reproduction
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ABN 77601754678

- CARSON, R.S., FINDLAY, J.K., CLARKE, I.J. and BURGER, H.G. Estradiol, testosterone and androstenedione in ovine follicular fluid during growth and atresia of ovarian follicles. *Biol. Reprod.* 24: 105-113, 1981.
- HURLEY, D.M., BRIAN, R., CLARKE, I.J. and BURGER, H.G. Induction of ovulation with subcutaneous pulsatile gonadotropin-releasing hormone: singleton pregnancies in patients with previous multiple pregnancies after gonadotropin therapy. *Fertil. Steril.* 40: 575-579, 1983.
- KEOGH, E.J., MEAKIN, J.L., BANOVIC, S., CURNOW, D.H., GILES, P.F.H., CLARKE, I.J. and WILSON, D. Ovulation induction with pulsatile gonadotrophin releasing hormone (GnRH). *Clin. Reprod. Fert.* 2: 175-189, 1983.
- CLARKE, I.J., WRIGHT, P.J., CHAMLEY, W.A. and BURMAN, K. Differences in the reproductive endocrine status of ewes in the early post-partum period and during seasonal anoestrus. *J. Reprod. Fert.* 70: 591-597, 1984.
- HURLEY, D.M., BRIAN, R., OUTCH, K., STOCKDALE, J., FRY, A., HACKMAN, C., CLARKE, I. and BURGER, H.G. Induction of ovulation and fertility in amenorrhoeic women by pulsatile low-dose gonadotropin-releasing hormone. *New Eng. J. Med.* 310: 1069-1074, 1984.
- DRIANCOURT, M.A., FRY, R.C., CLARKE, I.J. and CAHILL, L.P. Follicular growth and regression during the 8 days after hypophysectomy in the sheep. *J. Reprod. Fert.* 79: 635-641, 1987.
- HYLAND, J.H., WRIGHT, P.J., CLARKE, I.J., CARSON, R.S., LANGSFORD, D.A. and JEFFCOTT, L.B. Infusion of gonadotrophin-releasing hormone (GnRH) induces ovulation and fertile oestrus in mares during fertile oestrus. *J. Reprod. Fert. Suppl.* 35: 211-220, 1987.
- FRY, R.C., CLARKE, I.J., CUMMINS, J.T., BINDON, B.M., PIPER, L.R. and CAHILL, L.P. Induction of ovulation in chronically hypophysectomized Booroola ewes. *J. Reprod. Fert.* 82: 711-715, 1988.
- McNATTY, K.P., HENDERSON, K.M., FLEMING, J.S., CLARKE, I.J., BINDON, B.M., PIPER, L.R., O'SHEA, T., HILLARD, M.A. and FINDLAY, J.K. The physiology of the Booroola Ewe and Ram. 2nd International Workshop on Major Genes for Reproduction in sheep, Toulouse, France, Ed INRA Paris. pp 105-124, 1991.
- FINDLAY, J.K., CLARKE, I.J., LUCK, M.R., RODGERS, R.J., SHUKOVSKI, L., ROBERTSON, D.M., KLEIN, R., MURRAY, J.M., SCARAMUZZI, R.J., BINDON, B.M., O'SHEA, T., TSONIS, C.G. and FORAGE, R.G. Peripheral and intragonadal actions of inhibin related peptides. *J. Reprod. Fert. Supplement* 43: 139-150, 1991.

In particular, I have carried out work that investigated similar principles to those expounded by diZerega, as indicated in the following publication:-

- CAHILL, L.P., CLARKE, I.J., CUMMINS, J.T., DRIANCOURT, M.A., CARSON, R.S. and FINDLAY, J.K. An inhibitory action at the ovarian level of ovine follicular fluid on PMSG-induced folliculogenesis in hypophysectomized ewes. *Proc. 5th Ovarian Workshop (Laramie)*, Eds. D.O. Toft and R.J. Ryan, pp 35-38, Ovarian Workshops, Champaign, Ill. 1985.

I have carried out work on endocrinology of tamoxifen (which, like clomiphene is a triphenylethylene derivative with antiestrogenic properties) as outlined in the following publication:-

CLARKE, I.J. Effects of tamoxifen on plasma concentrations of luteinizing hormone and follicle-stimulating hormone in ovariectomized ewes. J. Endocrinol. 99: 23-29, 1983.

More recently I have carried out research on the compound referred to as "micrin" and described in the above patent application.

5. I have studied the Office Action sent by the examiner on 13 May 2004. I have also read and understood the cited reference US 4 734 398 (diZerega) and I was already familiar with diZerega's work, as indicated above.

6. Clomiphene is known to induce ovulation, if provided over a prolonged period of time, in women who are not ovulating. However, if sheep are provided with an acute administration of clomiphene within a few days after ovulation has occurred, as is described in the present patent application, this certainly does not cause further ovulation. The reproductive system is refractory to re-ovulation induction at this time, because the sheep would be in the luteal phase of the oestrous cycle, when progesterone levels are high; this prevents ovulation.

7. Indeed, clomiphene acts as a pure oestrogen in the sheep, at least at the level of the hypothalamo-pituitary axis. I have unpublished data to this effect. It is therefore probable that clomiphene would not induce ovulation in a sheep under any circumstances.

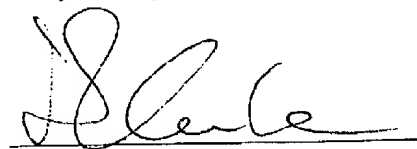
8. On the other hand, clomiphene does appear to induce the production of micrin, at whatever phase of the oestrous cycle it is administered. Micrin induction by clomiphene does not appear to be a secondary effect of ovulation, as it occurs whenever clomiphene is administered and regardless of when ovulation has occurred.

9. From my own immunohistochemistry experiments I have found that micrin can be found in brain tissues. This strongly suggests that that micrin is different from the compound described by diZerega.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that the statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of the application or of any patent issuing thereon.

Further declarant sayeth naught.

Signed:


Professor Iain Clarke

Date:

26 July 2004

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